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The Hippocampus, Memory, and Place Cells: Is It Spatial Memory or a Memory Space?

Review

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Identifying the scope and nature of memory processing by the hippocampus has proved a formidable challenge. The major initial insights came from studies of amnesia in human patients following removal of the hippocampus plus neighboring medial temporal structures (Scoville and Milner, 1957). The early studies indicated that this damage spares the initial acquisition of new information, but memory for all sorts of new information subsequently declines rapidly. More recent studies have shown that global amnesia results from limited damage within the hippocampus itself (Zola-Morgan et al., 1986) or including the hippocampus and dentate gyrus and sparing most or all of the surrounding cortex and other medial temporal structures (Vargha-Khadem et al., 1997). These findings indicate that the hippocampus plays a critical role in memory formation for a broad domain of information in humans.

Many studies have sought to clarify the nature of hippocampal information processing, using neuropsychological and electrophysiological approaches in animals. Among several proposals generated by these studies, one that has captured considerable attention is the view that the hippocampus mediates a neural representation of physical space, that is, a cognitive map (O'Keefe and Nadel, 1978). This theory was based on a thorough and systematic analysis of the expansive literature on diverse behavioral abnormalities following hippocampal damage. In addition, O'Keefe and Nadel's proposal incorporated a central observation about the behavioral physiology of hippocampal neurons, specifically that some cells increased firing rate when a rat was at a particular location in its environment (O'Keefe and Dostrovsky, 1971). The discovery of these place cells appeared to perfectly complement the findings on the behavioral deficits, showing that spatial information was encoded within the cellular activity of the very hippocampal structures that are necessary for spatial learning and memory.

Despite its appeal, the cognitive mapping theory, and in particular the findings on place cells, have had limited impact among neuropsychologists who study memory in humans and nonhuman primates. A major source of this limitation has been the contention that hippocampal processing is dedicated to spatial memory in rodents, in contrast to the global memory deficits observed following damage to the hippocampal region in humans and more recently in animals as well (Eichenbaum, 1997). Furthermore, several recent electrophysiological studies have revealed properties of hippocampal neuronal firing patterns that are inconsistent with the notion of a cognitive map and indicate a broader scope of information processing. This paper will focus on these studies, reviewing some of the history and basic properties of place cells, and considering both early and recent findings that shed light on the content and organization of information encoded within hippocampal neuronal activity. We will call into question the cognitive map account and offer an alternative view.

Why Place Cells Are So Compelling: Pointers in the Cognitive Map

In the early years of investigations on animal learning, proponents of the dominant "stimulus–response" ("S–R") theory argued that maze learning is mediated by a chain of direct associations between specific stimuli and rewarded behavioral responses. However, Edward Tolman (1948) provided compelling evidence that rats can navigate mazes using short cuts and roundabout routes to find goal locations, strategies that were not readily explained by S–R theory. Tolman concluded that rats create and use global representations of the environment, that is, cognitive maps, to localize goals in a maze. This view was criticized for the absence of evidence for a cognitive or neural mechanism that could underlie the cognitive map—something as compelling as the physiological observations on the conditioned reflexes that were viewed to mediate S–R learning. In the initial report on the discovery of place cells, O'Keefe and Dostrovsky (1971) recognized the potential significance of this neural correlate. Could these cells be the elements of the long sought, and much maligned, cognitive map?

Hippocampal place cells are fascinating to anyone who has witnessed the phenomenon. They are typically observed by monitoring extracellularly recorded action potentials from principal cells in CA1 and CA3 of freely behaving rats (Fox and Ranck, 1975). As the animal engages in behaviors across a large environment, one can readily correlate dramatic increases in a place cell's firing rate when the rat arrives at a particular location, called the "place field." From a baseline of <1 spike/s, the firing rate can exceed 100 Hz, although during some passes though the place field the cell may not fire at all. Typically, a large fraction of cells have place fields in any environment (Muller, 1996; Shen et al., 1997; Tanila et al., 1997a), although the low baseline firing rates may let many cells without place fields go undetected (Thompson and Best, 1989).

Place responses can be dissociated from potential confounding influences of particular behaviors that might occur at different locations. Olton and colleagues

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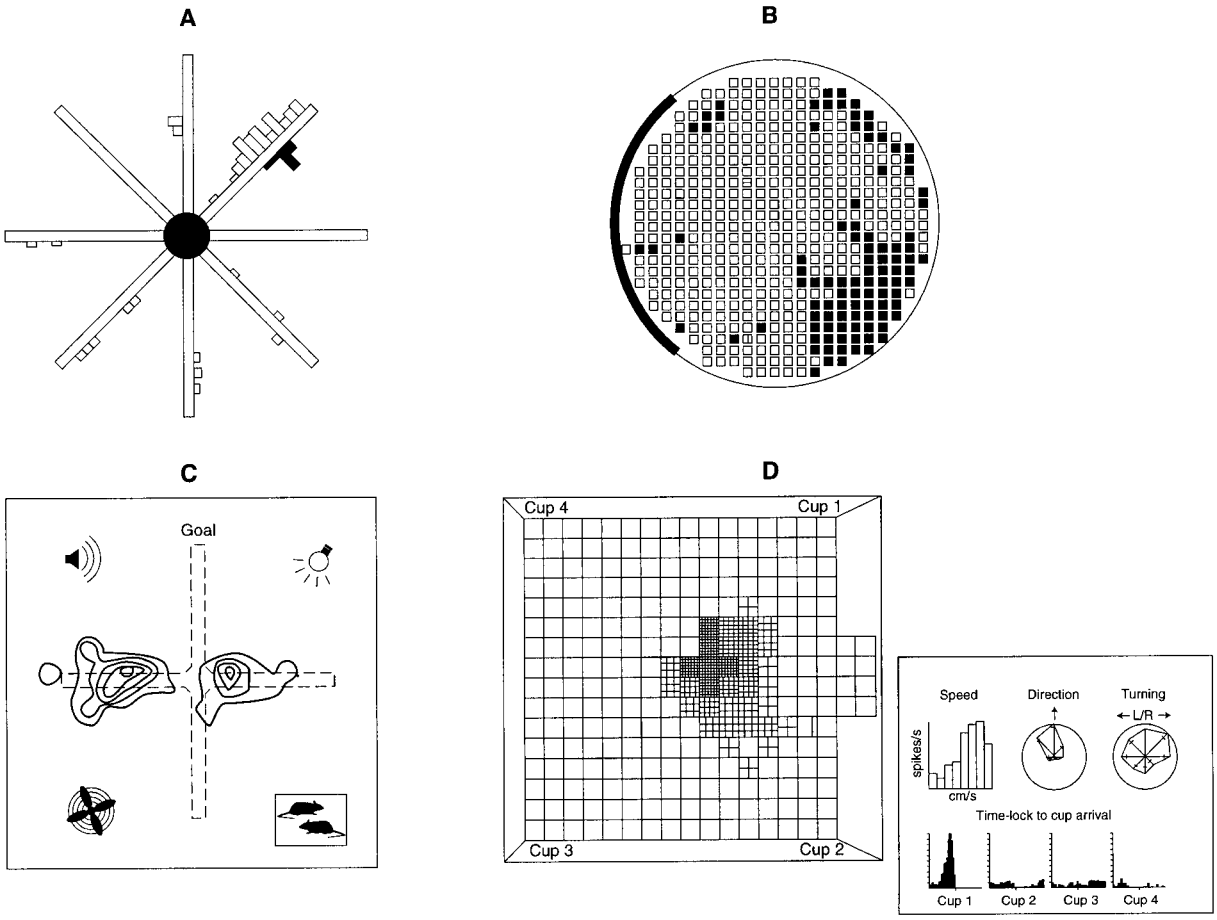

Figure 1. Schematic Overhead Views of Four Different Types of Apparatus and Examples of Location-Specific Activity of Hippocampal Place Cells

(A) Eight-arm radial maze, including bar graphs on either side of the maze arms showing firing rates of a place cell associated with inward (white bars) and outward (black bars) movements on each arm. From McNaughton et al. (1991).

(B) Cylinder, with the location of the cue card indicated by a thickened part of the circle, in which rats performed the random foraging task. The firing pattern of a place cell is indicated by open pixels at loci associated with low firing rates and closed pixels at loci associated with high firing rates. From Muller and Kubie (1987).

(C) Plus maze (dashed lines) surrounded by a blank curtain and four spatial cues. Contour plots indicate gradations in the firing rate of a cell with two place fields. From O'Keefe and Speakman (1987).

(D) Arena in which rats performed both a spatial working memory task and an olfactory discrimination task (at the cul de sac indicated by pixels at the right). The firing pattern of a place cell recorded while a rat performed the spatial task is indicated by increasingly filled pixels at loci associated with higher firing rates. Panels in the box to the right indicate the firing rate of the same cell associated with different speeds, directions, and angles of movement of the rat through the place field (top row, from left to right, respectively) and associated with time prior to arrival at each reward cup (bottom row). From Wiener et al. (1989).

(1978) observed hippocampal cellular activity in rats performing the same inward and outward traversals on all arms of a radial maze, and they found that many hippocampal cells fired only when the rat was on a particular arm (see also McNaughton et al., 1983; Figure 1A). Muller and colleagues (1987) more completely equalized behavior throughout an environment by observing hippocampal cellular activity in rats foraging for food pellets randomly dispersed in a circular open field (Figure 1B) and found location-specific activity of many of the cells.

Furthermore, the activity of many place cells is not dependent on any particular stimulus but rather reflects the presence and topography of multiple environmental cues. O'Keefe and Conway (1978) observed the responses of hippocampal cells to cue manipulations in rats performing a place discrimination on the elevated plus maze (Figure 1C). They found that many place cells maintained their spatial firing patterns when any one or two of the cues were removed, and they concluded that any subset of the cues sufficient to define their global configuration could support the location-specific activity. Muller and Kubie (1987) found that expansion of their circular open field caused some place fields to "scale up" in size but maintain the same shape and location, whereas altering the shape of the environment resulted in loss or unpredictable changes in spatial firing patterns. O'Keefe and Burgess (1996) showed that the shape and locus of place fields within a simple rectangular chamber are determined by the dimensions of, and spatial relations between, the walls of the environment.

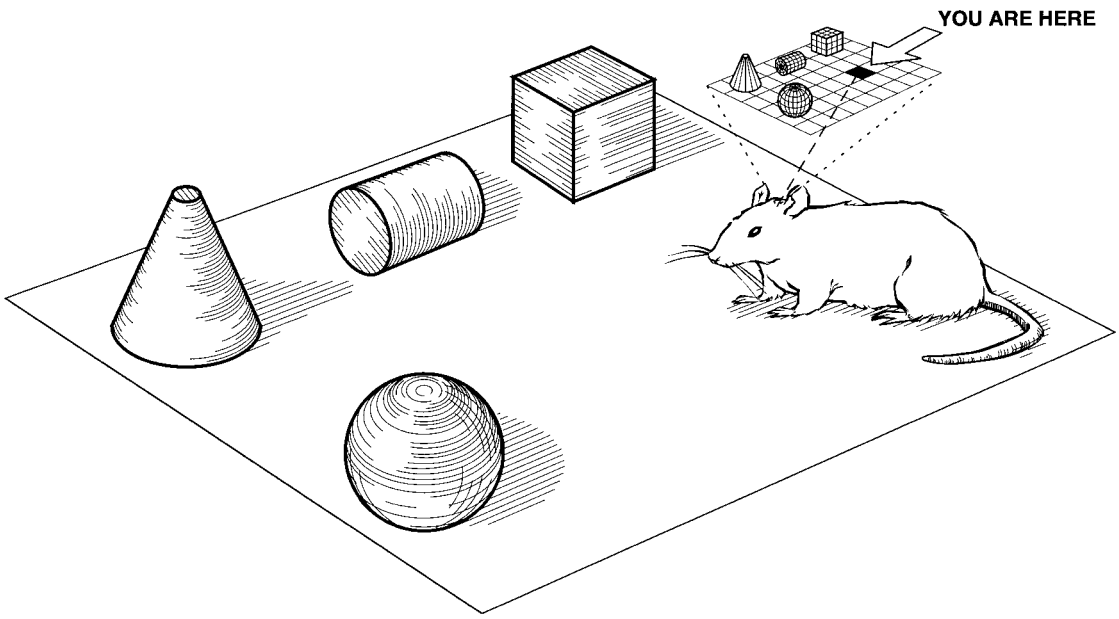

Figure 2. Cognitive Mapping

Conceptual model of hippocampal representation of a spatial environment according to the cognitive mapping hypothesis.

Each of these studies indicates that some hippocampal place cells encode cues about the topology of environments (see also Cressant et al., 1997).

Additional properties of place cells are consistent with features of spatial memory. Once established, place cells can have the same firing pattern for months (Thompson and Best, 1990). The firing patterns can persist even when all of the spatial cues are removed or the room is darkened (Muller and Kubie, 1987; O'Keefe and Speakman, 1987; Quirk et al., 1990), although the selectivity of spatial firing may be degraded in the dark (Markus et al., 1994). In an experiment where rats had to remember where removed spatial cues had been, errors in their choice behavior predicted shifts of their hippocampal place fields, suggesting that these codings were determined by the orientation of the maze remembered by the rat (O'Keefe and Speakman, 1987). These findings provide a compelling link between hippocampal spatial coding and spatial memory. All of these findings are consistent with O'Keefe and Nadel's (1978) notion of place cells as elements of a cognitive map that resides in the hippocampus.

The Structure of Cognitive (Spatial) Maps

Consistent with Tolman's (1948) description of a "cognitive-like map of the environment" (p. 192), the conception common to O'Keefe's (1979) characterization and to all modern accounts of the cognitive map is that the hippocampus contains a holistic representation of space (Muller, 1996), a facsimile of the environment including the salient environmental cues (Figure 2). This map constitutes an abstract coordinate grid of two-dimensional space, instantiated by a preconfigured network of intrinsic connections among hippocampal neurons (O'Keefe and Nadel, 1978; McNaughton et al., 1996; Samsonovich and McNaughton, 1997). The resulting map is Cartesian in that it provides metrics for the representation of distances and angles between the relevant stimuli. At the physiological level, a place cell reflects the occurrence of the rat at a particular coordinate position within the map. Thus, implicit in this model is the assumption that place fields can be considered "pointers" within a unified map. Finally, it should be clear that all models of the cognitive map involve exclusively allocentric spatial frameworks, that is, representations of space independent of the egocentric spatial information such as the animal's direction of movement. Observations of, for example, direction-selective spatial activity are considered an artifact of confusing multiple allocentric maps (McNaughton et al., 1996) or simply a result of different predictions about future location in the map depending on the direction of movement (O'Keefe and Burgess, 1996).

Details about the nature of the hippocampal spatial map have been modified in several recent models, and several mechanisms for its implementation have been offered. Worden (1992) proposed that the hippocampus fits codings of "fragments" of the environment into a cohesive representation of the environment. McNaughton and colleagues (McNaughton et al., 1996; Samsonovich and McNaughton, 1997) suggested that the metric for the map is self-motion. They and others (Redish and Touretzky, 1997) have suggested that during learning, representations of visual cues are bound to "charts" and serve as landmarks of a spatial reference frame for path integration. O'Keefe (1991) suggested that a polar coordinate system may be most effective for translating egocentric coordinates into an allocentric reference frame. More recently, Burgess and O'Keefe (1996) suggested a population vector model for navigation. O'Keefe and Burgess (1997) built a model of place representations based on distances from the walls of an environment. Blum

and Abbott (1995) proposed that intrinsic synaptic connections between place cells representing sequentially visited locations are asymmetrically potentiated during repeated motions, supporting the learning of paths. Muller et al. (1996) conceived that distances in a hippocampal "cognitive graph" are encoded according to distributions of synaptic strengths that arise through the differential timing of activations between place cells.

Summing up all these current models, several new proposals about the metrics and mechanisms of mapping and navigational computations have been generated since O'Keefe and Nadel's original proposal. However, the central features of the hippocampal cognitive (spatial) map remain fundamentally intact. Within all these accounts, cognitive maps involve a systematic, cohesive, allocentric coordinate framework into which environmental features are encoded (Figure 2). The dedicated function of this system is to determine an animal's location and to mediate navigational computations.

Place Cells, Yes—Spatial Map, No

The existence of location-specific activity of hippocampal neurons has been confirmed many times (see O'Keefe, 1979; Muller, 1996). However, as we will argue here, the evidence falls short of demonstrating that place cells are organized as a spatial map or that hippocampal neurons exclusively, or even primarily, encode spatial cues.

Hippocampal Spatial Representation: It's Less Than a "Map"

Morris (1990) pointed out that one major problem with the cognitive map view is the absence of evidence indicating how place cells that reflect only one's current location would guide movements to other important places. There are additional fundamental problems with the notion of place cells composing a map. Consider two central features of mapping illustrated in Figure 2. Systematic spatial maps are characterized by continuous and homogeneous representations of spatial loci, and these representations are bound together within a unified Cartesian framework. Evidence of these properties would provide a strong case for the cognitive map model. Yet, despite considerable effort, the evidence disconfirms rather than supports these properties.

Hippocampal Spatial Representations Are Not Continuous or Homogeneous

Identifying one's location throughout the environment requires that the entire space be represented, and most simply would be represented by a set of place fields distributed uniformly throughout the environment. Demonstration of a continuous and homogeneous representation of space onto hippocampal structure would provide compelling evidence for a fundamental spatial mapping function. However, even from the earliest studies, it was apparent that space is not represented this way within the hippocampus. Place fields are not continuously or topographically organized; instead, there is substantial evidence for a "clustering" of place fields of neighboring cells (Eichenbaum et al., 1989; Hampson et al., 1996), similar to the observation of clustered, nontopographic perceptual representations of complex visual properties in the inferotemporal cortex (Perret et al., 1987; Tanaka et al., 1991) and egocentric information in prefrontal and parietal associations areas (Funahashi et al., 1989; Tanila et al., 1993; Andersen, 1995). In addition, Hetherington and Shapiro (1997) observed hippocampal firing patterns in rats exploring an enclosed environment with a different prominent cue on each wall. They found that place fields systematically concentrated near the wall cues, rather than areas that lack predominant local stimuli. Furthermore, the place fields were more strongly controlled by a proximal cue, consistent with O'Keefe and Burgess' (1996) findings and indicating that a critical aspect of spatial firing is the distance from neighboring stimuli. These observations indicate that hippocampal representation does not involve a homogeneous representation of all the areas of physical space.

Hippocampal Spatial Representations Are Not Bound Together in a Cohesive Framework

If hippocampal activity reflects occupancy of a coordinate position within a systematic map, all place cells should encode position within the global topology of the environment, and these codings should be bound to one another within a holistic, cohesive spatial framework. However, several recent findings are inconsistent with these expectations, and instead the data indicate that hippocampal spatial firing patterns reflect independent representations of subsets of the spatial cues. For example, in Muller and Kubie's (1987) experiment (see above), the majority of cells lost or changed their place fields when the environment was expanded. In O'Keefe and Burgess' (1996) study, most of the place fields reflected distances from the closest walls, and none had the same place field in two boxes with the same shape but different size and a different firing pattern in two boxes of another shape. These findings indicate that overall topology was not the major influence for most cells in either of these studies.

Several recent studies have shown that place cells can encode subsets of the spatial cues and that these representations are not bound to other spatial representations in the same environment. Gothard and colleagues (1996a, 1996b) found that when a particularly salient cue or enclosure within an open field is moved repeatedly and randomly, the spatial firing patterns of some cells become tied to that cue. When rats were trained to shuttle between a mobile starting box and a goal location defined by landmarks in an open field, some cells fired relative to the static environmental cues, but others fired relative to a landmark-defined goal site or in relation to the start box. When rats were trained to shuttle between a movable start-end box and goal site on a linear track, the anchor of the spatial representation of many cells switched between these two cues, depending on which was closer. Under these conditions, the majority of the activated hippocampal cells did not exhibit location-specific activity that was associated with fixed environmental cues. Instead, their activity could be characterized as "spatial" only to the extent that they fired at specific distances from a particular stimulus or goal.

Shapiro, Tanila, and colleagues (Shapiro et al., 1997; Tanila et al., 1997a, 1997c) examined the responses of hippocampal cells to systematic manipulations of a large set of spatial cues. Different place cells encoded individual proximal and distant stimuli, combinations of

proximal or distant stimuli, or relations between proximal and distant cues. The place fields of some cells were fully controlled by as little as a single cue within a very complex environment, and most cells were controlled by different subsets of the controlled cues. Further examination of small ensembles of these cells recorded simultaneously confirmed that different cells were controlled by distinct subsets of the cues at the same time, indicating that the spatial representation was not cohesive (Tanila et al., 1997b). In several cases where two cells had overlapping place fields associated with one configuration of the cues, each cell responded differently when the same cues were rearranged. This finding shows that each cell was controlled by a different subset of the cues at the same time, and that their differential encodings are not due to shifts between two different spatial "reference frames" used by all cells at different times (Gothard et al., 1996b). Skaggs and McNaughton (1998) confirmed this finding by recording from multiple hippocampal place cells simultaneously in rats foraging randomly in two identical enclosures, between which they could move freely. Each hippocampal ensemble contained cells that had similar place fields and others that had distinct spatial firing patterns between the two enclosures. In this situation, some cells encoded the physical cues, whereas the activity of others at the same time reflected the knowledge that the two environments were distinct (for variants on this observation, see Bostock et al., 1991; Rotenberg and Muller, 1997; Jeffrey, 1998).

Combining the findings from all of these studies, it appears that place fields involve a collection of independent representations, each one encoding the spatial relations between some subset of cues. Spatial representations are not bound as coordinates within a systematic framework for the global topology, indicating that hippocampal spatial codings are not organized as elements of a Cartesian "map." The absence of a systematic mapping does not preclude the existence of a map elsewhere in the brain, or of spatial information in hippocampal representations, and indeed several models have shown that an animal's location and direction of movement can be estimated by vector summation of place cell activities (e.g., Burgess and O'Keefe, 1996; Blum and Abbott, 1995; Samsonovich and McNaughton, 1997). However, these models do not depend on, or provide support for, the existence of a systematic mapping of space in the hippocampus.

Hippocampal Representation: It's More Than Space

Even in his earliest description of place cells, O'Keefe reported that the spatial activity of hippocampal neurons was influenced by more than the location of the animal in the environment. O'Keefe and Dostovsky's (1971) first report emphasized that all the place cells fired only when the rat was facing a particular direction, and O'Keefe's (1976) detailed analysis described cells that fired only during particular behaviors including eating, grooming, and exploratory sniffing. These findings were consistent with Ranck's (1973) description of hippocampal cells that fired during orientating, approach, or consummatory behaviors. Nevertheless, the existence of nonspatial firing patterns has been largely ignored in subsequent studies on hippocampal place cells. Our aim is to highlight these findings and call into question the exclusivity of spatial representation.

"True" Place Cells in Rats Performing the Random Foraging Task

In Muller and Kubie's (1987) random foraging task performed in the open field (Figure 1B), most hippocampal neurons show spatially specific activity with no other remarkable behavioral correlates. Notably, this situation is unique in that it provides a set of conditions where spatial cues provide virtually the only regularities of the experimental protocol. The set of spatial cues provides the animal with a continuous salient orientation at all times that the animal is in the environment. By contrast, the delivery of rewards and the onset, direction, speed, and punctuation of movements and other behaviors are all fully and intentionally randomized in time and space in an effort to "subtract out" their influence. It is only under these highly restricted conditions that true place cells, neurons whose activity reflects the location of the animal regardless of variations in nonspatial stimuli and behavioral events, are observed. Notably, even in this situation most or all spatial firing patterns would fall short of meeting O'Keefe's (1979) original criterion of place cells as equally under the control of any subset of prominent spatial cues. In his own recent study using this protocol, most cells were controlled by only two of the four prominent cues and no cells were influenced by all of the cues (O'Keefe and Burgess, 1996).

Movement-Related Firing Patterns Emerge in Rats Performing Structured Locomotory Behaviors

In virtually all other protocols, where a variety of stimulus or behavioral regularities are imposed, hippocampal neuronal activity reflects the corresponding regularities embedded in the task protocol. These findings challenge the notion of a true place cell that reliably predicts the animal's location regardless of ongoing behavior. Consider the radial maze task, in which animals regularly perform runs outward on each maze arm to obtain a reward and then return to the central platform to initiate the next choice (Olton et al., 1978; McNaughton et al., 1983). Here, outward and inward arm movements reflect meaningfully distinct behavioral episodes that occur repetitively. Correspondingly, hippocampal neurons reflect the relevant "directional structure" imposed by this protocol, and almost all place cells fire only during outward or inward journeys (Figure 1A). Similarly, place cells are activated selectively during distinct approach or return episodes and from variable goal and start locations in open fields and linear tracks (Wiener et al., 1989; Gothard et al., 1996a, 1996b).

Wiener et al. (1989) extended these findings to rats performing a radial maze–like task within an open field (Figure 1D). They found that the majority of place cells fired differentially during outward or inward traversals and were tuned for a particular speed of movement and angle of turning through the place field. Markus et al. (1995) directly compared the directionality of place cells under different task demands, and they found that place cells that were nondirectional when rats foraged randomly in an open field were directional when they systematically visited a small number of reward locations. Taken together, these findings emphasize that place cells exhibit movement-related firing patterns whenever particular movements are associated with meaningfully

different events (see also Muller et al., 1994). Whereas some investigators have modified the spatial mapping account to incorporate self-motion as an important parameter of hippocampal representation (Foster et al., 1989; McNaughton et al., 1996), self-motion is not essential to the firing of place cells (Gavrilov et al., 1998). Thus, whereas hippocampal cells appear to incorporate a variety of movement-related cues (including inertial cues; Sharp et al., 1990, 1995; Knierim et al., 1995, 1998; Wiener et al., 1995; Bures et al., 1997; Jeffery et al., 1997), we will argue below that these comprise only part of the information coded by the hippocampus.

Hippocampal Neuronal Activity Represents Nonspatial Stimuli, Cognitive Demands, and Learned Behavioral Responses

The above described studies show that when the experimental protocol introduces regularities that involve nonspatial features, such as regularly performed actions in particular places and different kinds of experiences within the same environment, place cell firing patterns can be dramatically affected. In parallel with these findings, other studies have shown that the firing patterns of hippocampal neurons can be related directly to the occurrence of nonspatial stimuli and behaviors in animals performing tasks where these nonspatial events occur with regularity. Thus, consistent with some of the early findings, experiments that have investigated event-related neural activity have demonstrated firing patterns of hippocampal neurons directly related to nonspatial stimulus, cognitive, and behavioral events.

In rats and rabbits performing different classical conditioning tasks, a large fraction of hippocampal neurons fire strongly associated with the learned significance of stimuli and with learned responses (Olds et al., 1971; Segal and Olds, 1972; Segal et al., 1972; Berger et al., 1976; Berger and Thompson, 1978; McEchron and Disterhoft, 1997). Hippocampal cells begin to fire early in training, prior to the appearance of the conditioned responses, and the responses of individual cells can be related to the timing of stimuli and conditioned responses (Berger et al., 1983; McEchron and Disterhoft, 1997).

A large fraction of hippocampal neurons are also activated in animals performing a variety of instrumental learning tasks that involve discriminations among olfactory, visual, or auditory stimuli (Eichenbaum et al., 1987; Wible et al., 1986; Wiener et al., 1989; Sakurai, 1996) and delayed matching- and nonmatching-to-sample tasks that test recognition memory (Wible et al., 1986; Sakurai, 1990, 1994, 1996; Otto and Eichenbaum, 1992; Hampson et al., 1993; Young et al., 1994; Deadwyler et al., 1996; Wood et al., 1999; reviewed by Olton, 1989). Different neurons are activated during virtually every moment of task performance, including during approach and stimulus sampling behaviors, discriminative responses, and consummatory behaviors. Some cells show striking specificities reflecting the coding of stimulus spatial or temporal configurations, whereas others show striking generality, observed either as prolonged activation across a sequence of trial events or as firing associated with a variety of stimuli or reward contingencies. In addition, the activity of some cells reflects the relevant cognitive demands of the task, for example, the match or nonmatch relationship between stimuli when a judgment between these is required. The nonspatial firing patterns of hippocampal neurons are as robust as spatial firing patterns, whenever the neural activity can be closely time-locked to critical sensory or behavioral events (e.g., Berger et al., 1983; Wiener et al., 1989). Finally, the prevalence of spatial and nonspatial firing patterns is also comparable in studies where the incidence of both types of coding was evaluated (Wible et al., 1986; Young et al., 1994; Wood et al., 1999).

The nonspatial firing patterns of hippocampal neurons are as easily observed in behavioral tasks that do not depend upon the integrity of the hippocampus as they are in situations where the hippocampus is necessary for performance. For example, nonspatial firing patterns were as robust and as prevalent in hippocampal cells recorded from animals performing a discrimination task where performance is disrupted by hippocampal damage (Wiener et al., 1989) as in a variant of the same task where hippocampal damage has no effect (Eichenbaum et al., 1987). Similarly, robust hippocampal neuronal responses are observed in variants of classical eyelid conditioning that do or do not require an intact hippocampus (Berger et al., 1983; McEchron and Disterhoft, 1997). Notably, this situation parallels the finding that place cells are as readily observed in rats during random foraging or other spatial tasks without a memory demand (McNaughton et al., 1983) as they are in animals performing a hippocampal-dependent radial maze task (Olton et al., 1979). Thus, both nonspatial and spatial representations by hippocampal neurons are "automatic" in the sense that they arise regardless of whether task performance depends on hippocampal function.

Finally, true place cells have not been observed in primates, although various types of sensory- and response-related activity is often gated by egocentric or allocentric spatial variables (Rolls et al., 1989; Feigenbaum and Rolls, 1991; Ono et al., 1993; O'Mara et al., 1994). In humans, visually evoked responses of hippocampal neurons have been observed (Halgren et al., 1978), and a substantial fraction of these cells fired on the sight of a particular word or face stimulus or during execution of task-relevant key press responses (Heit et al., 1988, 1990). In a more recent study, Fried et al. (1997) characterized a substantial number of hippocampal cells that responded to visual stimuli presented in a recognition task, including cells that differentiated faces from objects, distinguished facial gender or expression, or distinguished new versus familiar faces and objects. The largest fraction of cells differentiated combinations of these features. Some of the cells had a specific pattern of responsiveness across all of these parameters. Thus, the data from nonhuman primates and human subjects are consistent with the broad scope of nonspatial codings observed in studies on rats.

Nonspatial Firing Patterns Can Emerge Independent of Spatial Location

In nearly all of the studies reviewed above, the task-relevant stimuli and behavioral events occur in unique locations. Therefore, it might appear that the activation of these cells reflects the locations where particular important events happen. However, in these studies location alone was not sufficient to account for activation of hippocampal cells associated with nonspatial stimuli

and behaviors. For example, in Eichenbaum and colleague's studies (Eichenbaum et al., 1987; Wiener et al., 1989), some hippocampal cells became active only when the rat was at a stimulus port, but these cells only fired as the animal sampled the stimuli and ceased firing abruptly as the response was completed, even though the animal's position was identical to that during the sampling period.

In addition, there is now a direct demonstration of nonspatial activation of hippocampal neurons regardless of spatial location (Wood et al., 1999). In this study, rats were trained to perform an odor-guided nonmatch-to-sample task in which specific olfactory cues were moved systematically among several locations within a static environment. In this protocol, only a small proportion of the location-selective cells fired associated with only the position of the odor, and less than half of the active cells demonstrated a spatial component of firing conjointly associated with nonspatial factors. The firing of most of the active cells was associated with one or more nonspatial factors at all locations: the approach to any odor, specific odors, or their match/nonmatch status. In this protocol, a substantial number of hippocampal neurons encoded each prominent nonspatial regularity of the task across many locations. These findings provide unambiguous evidence that the representation of nonspatial stimuli is not necessarily ancillary to spatial coding but rather reflects nonspatial regularities that occur independent of location.

Conceptual Reorientation: The Content, Organization, and Functional Role of Hippocampal Representations

There was justified excitement about the discovery of place cells, particularly about the properties of these cells that called for a "cognitive" rather than a purely sensory or motor characterization. However, the conclusion that these firing patterns reflect elements of a Cartesian map of space has not been demonstrated. In addition, multiple lines of evidence are inconsistent with the idea that hippocampal cells are dedicated to spatial coding and instead indicate that their scope of representation extends to the full range of regularities present in the experience (Table 1). The following proposal rejects the notion of the cognitive map and offers a different characterization of the content and organization of hippocampal representation. First, we will suggest mechanisms that could mediate the development of a broad range of contents in these codings. Second, we will suggest that hippocampal neurons represent the sequence of events that compose ongoing behavioral episodes, and that repeated and related episodic representations can be used to build a memory space in the hippocampus. Third, we will consider how a memory space could mediate properties of hippocampal-dependent memory.

The Content of Information Encoded in Hippocampal Neural Activity

Here, we propose that individual hippocampal cells encode regularities present in the animal's every experience, including spatial and nonspatial cues and behavioral actions. During his pioneering studies on hippocampal neuronal activity in behaving animals, James Ranck, Jr. (1973) observed nonquantitative but consistent firing patterns of hippocampal neurons related to a very broad variety of stimulus and behavioral events, and he suggested (only half in jest) that any appropriately structured task would reveal neurons whose activity reflects precisely those variables critical to one's theory (personal communication). Is the puzzle of place cells resolved simply by characterizing hippocampal neuronal activity as a "mirror" of the relevant stimuli and behaviors in any behavioral paradigm? This characterization fits remarkably well both with the breadth of the data described above and with Morris and Frey's (1997) suggestion that the hippocampus automatically encodes all attended experiences. How can the hippocampus perform such a task?

The Development of Hippocampal Codings

We presume that each hippocampal cell is capable of diverse types of coding because of the different inputs these cells receive. The distribution of cortical inputs onto the longitudinal axis of the hippocampus is very broad, and the longitudinal association pathways in the hippocampus allow recurrent connections among hippocampal neurons (Amaral and Witter, 1989). At the same time, different specificities would be expected to develop among cells because the cortical inputs arrive in a graded topography such that each cell receives a different combination of plastic input weights. We propose that when particular combinations of inputs that significantly influence a cell cooccur within the time frame of Hebbian cooperativity ($\sim$200 ms), the synaptic strengths of those inputs in driving the cell are altered (e.g., Bliss and Lynch, 1988). Consequently, this conjunctive coding for a particular combination of stimulus and behavioral features constitutes the representation of a distinct "event." It is possible that the number of repetitions required to produce event codings may be quite small, and they may occur even after a single presentation under appropriate conditions, truly reflecting learning of events within a unique episode (Rose and Dunwiddie, 1986; Huerta and Lisman, 1995). Indeed, hippocampal representations form within minutes and are stable for months, and the stabilization of place fields is prevented by blocking long-term potentiation (Austin et al., 1990, Soc. Neurosci., abstract; Rotenberg et al., 1996; Cho et al., 1998; Kentros et al., 1998). Thus, according to this conception, different specificities of cells arise from the combination of diverse initial input weights and the particular history of coactive inputs to each cell that strengthen some of these inputs.

Some hippocampal codings are extremely selective to a particular combination of regularities, for example, to the occurrence of a particular odor only when it has a particular significance and is experienced in a particular place (Wood et al., 1999). These neurons seem to encode nearly unique events that occur very occasionally. In addition, though, other neurons have firing patterns that are broader in one of two ways. The selective activity of some neurons is broader in time, such that they fire for a more prolonged period, throughout a series of behaviorally distinct events that occur in sequence during repetitive behaviors (Eichenbaum et al., 1987;

Table 1. Properties of Hippocampal Neural Activity

(1) The environment is not encoded in a continuous and systematic representation within the hippocampus. Instead, the codings of spatial and nonspatial features are organized in "clusters" of neurons that overrepresent some features of the environment at the expense of others.

(2) Hippocampal spatial firing patterns do not reflect the global topology of all the attended environmental cues. Instead, individual cells encode the relevant spatial relations among particular subsets of the cues.

(3) Hippocampal spatial firing patterns do not consistently represent the animal's position among cues that compose an environment. Instead, the hippocampus creates distinct spatial representations, even for the identical spatial cues, under a variety of conditions where the animal might consider itself undergoing different experiences within the same environment.

(4) Within a broad variety of protocols in which animals learn regularities between stimuli, behavioral responses, and reinforcers, hippocampal neurons encode nonspatial stimuli and behaviors. These nonspatial firing correlates can be as robust and as prevalent as spatial firing patterns and, in a behavioral paradigm where distinctive events are distributed around the environment, they can be observed at all places where the associated events occur with regularity.

(5) The activity of many of the cells reflects the relevant spatial and nonspatial features of the task, whether or not the task is one that depends on hippocampal function.

(6) Both spatial and nonspatial representations are established very rapidly within the hippocampus.

(7) Hippocampal neurons are activated during every phase of the performance of spatial and nonspatial tasks.

(8) Hippocampal neuronal activity reflects a broad spectrum of specificities. Some cells encode unique events, characterized by particular conjunctions of stimuli, behaviors, and the locations where these occur. Other cells represent sequences of events within behavioral episodes or specific features of events that are common across different behavioral episodes.

Wiener et al., 1989; Gothard et al., 1996b; Mehta et al., 1997). Other hippocampal codings incorporate a broader set of events that share a common feature across experiences, such as an odor that is experienced in many places or a place where different events occur (Wood et al., 1999).

In the present conception, all of these codings arise from the same general Hebbian mechanism and differ only in the nature and number of the afferents that are regularly activated together, and in so doing become part of their representation. According to this scenario, initial experiences produce relatively weak but highly specific codings for particular conjunctions of the stimuli, behavioral actions, and places that cooccur within the brief Hebbian time frame. Successive repetitions of similar experiences then shape the nature and specificity of each neuron's responsiveness. The more broadly tuned cells that fire across a sequence of events may be those that initially receive inputs associated with events that happen to be successive or overlapping in the task protocol. In these cases, the repetition of these events in sequence serves simply to strengthen prolonged firings. Alternatively, some cells may initially become engaged by stimuli and behaviors associated with a punctate event, but when repetitive behavioral experiences produce regularities in the sequence that include other initially weaker inputs, the firings become gradually prolonged through the multiple events (Mehta et al., 1997). The broadly tuned cells that fire associated with common events across different episodes may receive dominant input from only one source of active features of a task that are present across different experiences. Alternatively, these cells might receive multiple inputs associated with diverging stimuli and events that occur across different episodes. During initial experiences, a weak selectivity for a particular combination of features might occur, but subsequently the accumulated noncoincident activations for some features might "cancel" such that eventually only the common stimuli, actions, or locations that occur reliably control the cell's activity.

The Organization of Hippocampal Representations

Above, we argued that the regularity of events in time determines the information encoded by hippocampal neurons (see also Wallenstein et al., 1998). In addition, two aspects of hippocampal firing patterns described above offer strong clues about how they might be organized within patterns of activity of the full hippocampal network. First, in virtually every spatial and nonspatial testing protocol, a subset of hippocampal neurons is selectively activated at every moment throughout task performance, suggesting a continuous and automatic recording of experiences (Morris and Frey, 1997). Second, the broad range of selectivities of individual hippocampal codings suggests mechanisms for linking representations of distinct events across short segments of time and across different experiences when similar events occur.

We propose that these coding specificities reflect different functional elements that build a memory space, a network of interconnections among the representations of both rare and common events. The basic building blocks of the memory space are conceived as the *event* codings described above, the highly specific, conjunctive representations that reflect features of particular episodes of behavior. The two broader types of codings are conceived as serving two different purposes in linking the events. The codings that are broader in time encode the temporal *sequence* in which a set of temporally punctate events compose particular behavioral episodes. The codings that are broader in the features represented encode the spatial and nonspatial regularities of the experience that are shared across different episodes in the same behavioral situation and, as such, may represent *nodes* that cross between distinct behavioral episodes. Together, the prototypical event, sequence, and nodal representations compose the memory space of interconnections in the hippocampus (Figure 3).

The Record of Experience: Linking Events within Episodes

We suggest that the coding of spatial locations by hippocampal place cells emerges from a fundamental representation of behavioral episodes. These representations involve a network of cells, each of which represents a temporally defined event. To envision how this coding of episodes unfolds, one must adopt a novel perspective

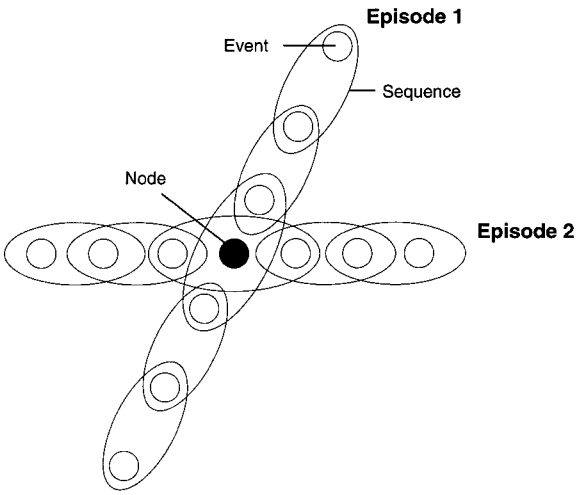

Figure 3. A Simple Memory Space

Conceptual model illustrating different hippocampal neural coding properties according to the memory space concept.

about place cell activity. The current convention is to describe place cell firing as a set of fundamentally location-coded activations distributed around an environment, sometimes with secondary influences such as the speed and direction of movement, and rarely other factors (Wiener et al., 1989; Figure 1D). Alternatively, as illustrated in Figure 4A, the activity of many of these cells could equally well, and more simply, be characterized as a set of activations along a temporal sequence as the rat moves in different trial episodes. This description suggests that the appearance of movement-modulated spatial firing is better characterized as a representation of an action sequence, where the network of place cells encodes distinct views and movements that together compose the journeys to and from important places (see Wilson and McNaughton, 1993; Gothard et al., 1996a, 1996b; McHugh et al., 1996).

This characterization equally applies to the various learning tasks described above. As animals perform each of these tasks, individual hippocampal cells fire at every phase of task performance, observed as neural activity time-locked to each identifiable stimulus and behavioral event. For example, as illustrated in Figure 4B, individual cells in rats performing an odor discrimination task fired at different times associated with the approach to the odor sampling port, during the odor sampling period, and during the discriminative response and reward period (Eichenbaum et al., 1987). Importantly, we are expanding beyond the usual characterization of hippocampal neurons as a collection of cells that encode the independent occurrence of different cues (or places) and behaviors. We are proposing that, at the population level, the hippocampus encodes each behavioral episode by a sequence of event representations, with each event characterized by a particular combination of spatial and nonspatial stimuli and behavioral actions.

How these event codings are connected to compose the representation of entire behavioral episodes has been considered in earlier theoretical and computational proposals (Hetherington and Shapiro, 1993; Levy, 1996; Wallenstein et al., 1998; Lisman, 1999). These accounts have proposed the necessity for two of the types of codings within the hippocampal network introduced above. Some representations reflect a temporally punctate event, whereas other representations involve multiple successive events that compose a sequence (or temporal "context"), as introduced above. For example, the activity of the cell marked by a short arrow in Figure 4 continued throughout the sequence of behaviors associated with odor sampling and behavioral choice during episodes of an odor discrimination task. Notably, the sequence representations would be specific to particular types of episodes in a task to the extent that they incorporate the details of its particular events. Sequence codings could "bridge" representations of distinct events that make up an episode, by overlapping with and consequently activating other event and sequence codings for later parts of an episode. Such a scheme can be used to predict or replay the details of episodes ("pattern complete") when cued by presentation of the initial events, consistent with models of hippocampal autoassociation beginning with Marr (1971) and since then elaborated in several different ways (McNaughton and Morris, 1987; Rolls, 1987, 1996; Willshaw and Buckingham, 1990; Recce and Harris, 1996). In addition, such schemes can be used to disambiguate ("pattern separate") related but different episodes that share ambiguous features (Gluck and Myers, 1993; Shapiro and Olton, 1994; Levy, 1996; Wallenstein et al., 1998; Lisman, 1999).

Building a Memory Space: Linking Repeated and Related Episodes

Now we will consider how episodic codings might be employed in building an even larger network that links each episode to other related episodes within the overall context of experience. The following considerations extend the scheme to incorporate the "nodal" cells that respond during events that are common across all the different types of trials within any particular task. We propose that these neurons encode the intersections among otherwise distinct episodes that have in common the stimulus configuration that defines a particular place, a particular nonspatial stimulus or stimulus relationship, or the execution of a particular behavior. These nodal representations link different episodes that share common features. For example, a true "place cell" links episodes that occurred in the same location, and an "odor cell" links episodes in which the same odor was perceived (Wood et al., 1999).

Studies that involve examination of the same neurons in animals performing two variants of the same experimental protocol provide compelling evidence that some hippocampal cells encode the separate events that distinguish the variants, and others encode the events that are common between them. For example, in their study of place cells in rats performing a radial maze task, Shapiro, Tanila, and colleagues (Shapiro et al., 1997; Tanila et al., 1997a, 1997c) repeatedly exposed rats to a standard configuration of distal and local cues and a variant where the sets of distal and local cues were rotated 90° in opposite directions (Figure 5). Over many presentations of both conditions, the place fields redistributed. Some cells acquired distinct representations in the two conditions, whereas all other cells converged on the same representation of either the distal cues, the local cues, or the fixed cues. Thus, part of the hippocampal network captured the unique events within each

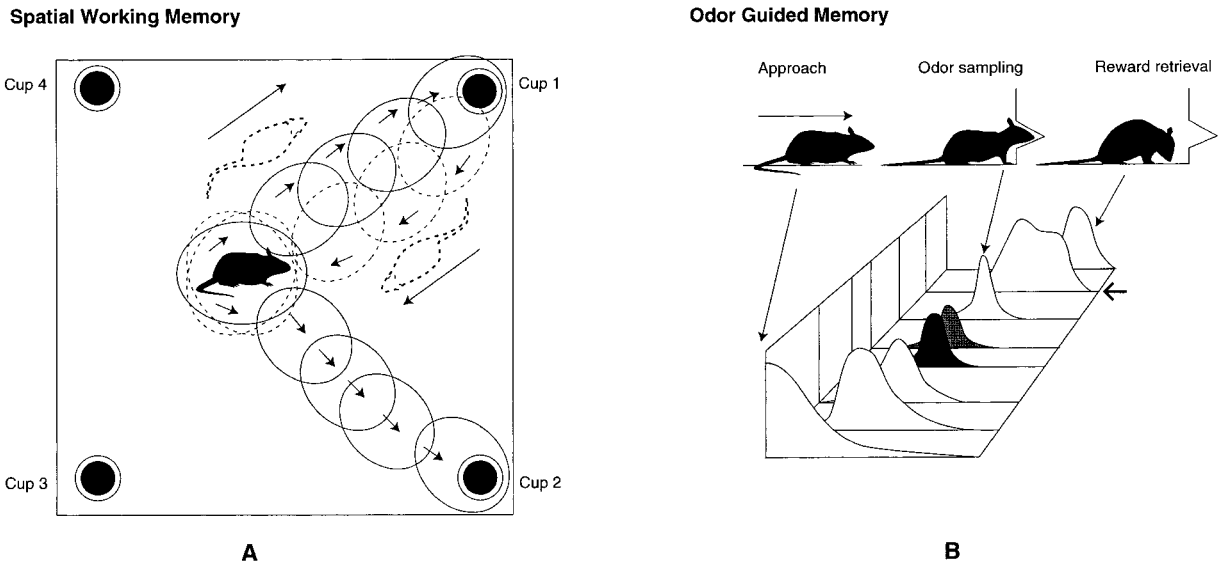

Figure 4. Idealized Neuronal Firing Patterns of an Ensemble of Hippocampal Neurons

(A) Firing patterns of place cells from a rat performing a spatial working memory task in an open arena. Arrows indicate directionality of each place cell (see Wiener et al., 1989).

(B) Nonspatial firing patterns of cells from a rat performing an olfactory discrimination task (see Eichenbaum et al., 1987). Each panel illustrates the increased firing of a cell at a particular time during trial performance. The two curves with different closed patterns indicate cells that fire only during the presentation of a particular odor configuration. The arrow at the right of one curve indicates a cell that encodes the sequence of odor sampling and the behavioral response.

distinct condition, whereas others captured a set of regularities in stimulus relations that were common across both conditions—the nodal features. Consistent with these observations, other studies have also shown that different subpopulations of simultaneously recorded place cells represent either the common features or distinct experiences associated with closely related environments (Markus et al., 1995 [see Figure 9]; Skaggs and McNaughton, 1998; see also Quirk et al., 1990 [see Figure 5]; Markus et al., 1994).

The present account puts the hippocampus as central to episodic memory. At the same time, this proposal also composes episodic representations as tied to one another within a general memory organization, consistent with the common notion that networks of semantic knowledge are built from episodic experiences. These aspects of hippocampal functional organization are illustrated in our simple model (Figure 3), in which episodic representations are composed as nonoverlapping event codings, linked by overlapping sequence codings. In addition, the episodic representations that share an event can contain a nodal element that links them. Sequence codings contained in only one episodic representation can provide a mechanism to disambiguate the two episodes, by linking the events going into and out of the nodal point. In addition, the nodes provide a basis for linking and crossing over between episodes when warranted by task demands that require reference across separate experiences (Levy, 1996; Wallenstein et al., 1998). The set of all linked episodes we call a "memory space." Importantly, the notion of a memory space differs fundamentally from that of a cognitive (spatial) map in that the organizing principle is the sequence of events in time, not spatial relations between objects in the physical environment.

Testing the Memory Space Hypothesis

The memory space hypothesis was created in an effort to explain the considerable body of evidence described above that is contradictory to the cognitive mapping view. For example, the cognitive mapping account fails to account for why a large proportion of hippocampal neurons fire selectively associated with nonspatial stimuli, actions, and cognitive events that occur at many locations in the same environment (Wood et al., 1999). By contrast, within the memory space hypothesis, these firing patterns encode configurations of stimuli and actions that compose events that occur reliably in meaningful behavioral episodes. The memory space hypothesis also accounts for the broad range of specificities of hippocampal codings, including cells that encode combinations of features that compose a unique event, codings that bridge between events in a sequence, and cells that encode nodal events (e.g., places, odors) that are common across behavioral episodes.

In addition, the memory space hypothesis accounts for several situations where hippocampal cells are unreliable indicators of the animal's location, such as when place cell activity is modulated by movement direction and speed. Within the memory space hypothesis, movement direction and speed, as well as other behavioral events, serve to better characterize the combination of stimuli and actions that are incorporated into hippocampal codings. Along the same line, the memory space hypothesis accounts for why hippocampal cells sometimes dramatically change their firing patterns when the animal performs different tasks in the identical environment (Wiener et al., 1989; Markus et al., 1995). In these cells, it appears that the common spatial features of the tasks are not sufficient to determine the cell's activity.

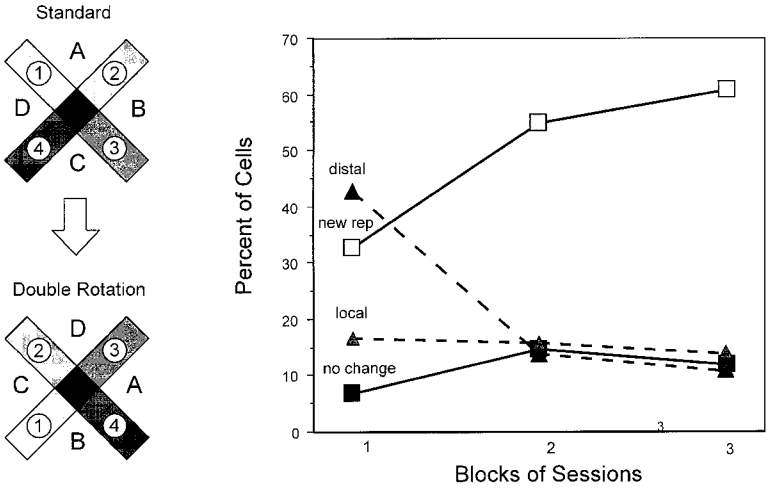

Figure 5. Plasticity in CA1 Population Representations

Proportions of the hippocampal neural population that encode different types of cues as rats perform a spatial memory task in a plus-shaped maze (1–4 indicate local cues; A–D indicate distal cues). Over a series of recording sessions, the animal experienced repetitive alternations of the standard configuration and double rotation configuration of the same cues ("new rep," new representation).

Rather, the cell is under the control of different motivational or other behavioral aspects that are distinct between the different episodes performed in the same environment.

When spatial or nonspatial features are changed in a familiar situation, the cognitive mapping view suggests that the entire hippocampal ensemble must act coherently, such that all the place cells either maintain the same firing pattern or all the cells form a new representation (a complete "remapping"; Muller, 1996). By contrast, the memory space hypothesis predicts that when cues are altered in a familiar environment there will be only a partial recoding. According to this view, some cells will maintain the same firing patterns, as long as the spatial or nonspatial features coded by those cells are not disrupted by the change. Other cells will change their firing patterns if the configuration of cues that control them is altered. This pattern of findings has now been confirmed in several recent studies (see Figure 5; Markus et al., 1995; Shapiro et al., 1997; Tanila et al., 1997c; Skaggs and McNaughton, 1998). We predict that the preserved codings will be observed immediately when the environment changes, whereas the new codings will develop gradually over a short period of experience with the new cue arrangements—this aspect of the recodings has not yet been examined.

The memory space hypothesis also generates several other new testable predictions about hippocampal neural firing patterns. In our description of the development of hippocampal codings (see above), we suggested that the encoding of conjunctions of cues and behaviors arises from Hebbian learning mechanisms. Following this suggestion, it is expected that when a rat is introduced to a new situation, hippocampal neurons will show relatively small responses to spatial and nonspatial features of the situation. We expect that the responses will become more robust and more selective associated with repeated experience with the same combination of spatial or nonspatial features.

Other predictions follow from our proposal that some hippocampal cells encode events and sequences that are distinct between related episodes, whereas others encode the common nodal events (Figure 3). A specific prediction is that some hippocampal cells will have different firing patterns associated with distinct behavioral episodes within one behavioral task, even at times when the animal is in the same place and moving in the same direction under the same overall motivation. For example, imagine a rat performing a standard T maze spatial alternation task in which it initially runs on a common stem of the T, and then on different episodes alternates between a left or right turn at the end of the stem in order to receive rewards. In this situation, we predict the existence of hippocampal cells that fire on the common stem only when the rat is in the midst of a right-turn episode and not a left-turn episode, and vice versa. These cells cannot be described as true place cells, because they do not fire reliably when the animal is in a particular location. And their activity cannot be explained by egocentric spatial factors, because on both types of episodes the rat is running with the same direction and speed. Rather, the predicted firing pattern is consistent with the coding of a particular event or sequence within the right- or left-turn episode. This coding could serve to disambiguate the two kinds of episodes in the alternation task. In addition, we predict the existence of other hippocampal neurons that have the same firing pattern in both types of episodes. These cells would reflect the nodal features of the events that are common across the two kinds of episodes, such as running in a particular direction at a particular place.

The converse prediction involves the expectation that cells that initially have selective codings to combinations of events can, through experience, develop nodal codings of features that are common across episodes. For example, if a rat were initially trained to guide its behavior according to a particular odor at only some locations in the environment (or in only one environment), we would expect the firing of these cells to occur in only that part of the environment (or in only that environment). However, after extended experience in which the odor has the same significance across all locations (or across many environments), we would expect the observation of some nodal cells that show the same pattern throughout the environment (or across environments). The predictions offered here provide examples of a general framework for distinguishing between the cognitive mapping account and the memory space hypothesis based on dissociating spatial (as well as nonspatial)

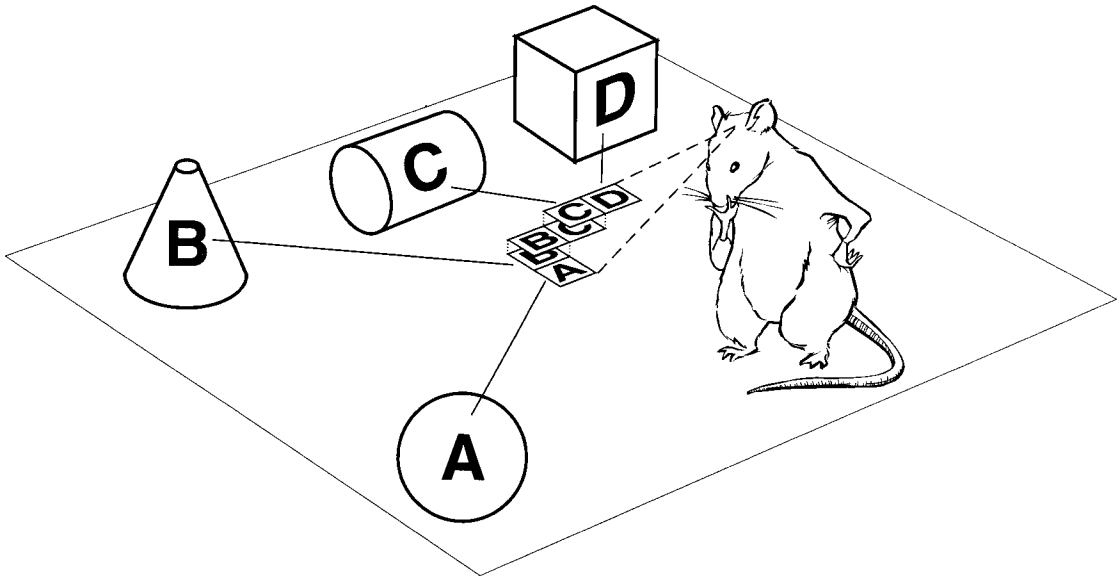

Figure 6. Relational Coding of Space

Representation of a spatial environment by cells that encode the spatial relations between a pair of the cues (AB, BD, or CD), plus nodal representations (dotted lines) for the cues that are common between some pairwise codings.

firing patterns according to the episodic context in which they occur.

The Role of Hippocampal Representations in Memory Performance

What role does a hippocampal memory space play in memory performance? In this section, we will first suggest how the properties of the memory space described above might mediate central features of hippocampal-dependent spatial and nonspatial memory in animals. Second, we will consider how the properties of the hippocampal memory space could support the phenomenon of memory consolidation.

Flexible Memory Expression

A central property of hippocampal-dependent memory is the capacity to express memory "flexibly," to employ memories obtained in one set of circumstances to solve new problems (Cohen and Eichenbaum, 1993; Squire et al., 1993). Particularly useful examples of the flexibility of declarative memory in animals involve the capacity to navigate in space and to make inferential judgments based on information obtained in different episodes.

Spatial Navigation. In the present account, spatial memory capacities are viewed as the byproduct of a large set of event, sequence, and nodal representations for spatial features that are encoded during behavioral episodes in an environment. Within this view, individual hippocampal cells encode small sets of cues and their spatial relations, as well as other aspects of behavioral events, at each point in a sequence of experiences in the environment. As more and more episodes are executed, with the animal crossing the same locations while executing different behaviors, a greater number of nodal representations capture the spatial regularities that cut across distinct episodes. The consequent representation of space is constituted as a large collection of nodal codings that overlap the episodic representations, determining and constraining the overall representation of spatial relations among the cues.

In an illustration of this model (Figure 6), each cell is conceived as coding only two cues in terms of their spatial relationship as viewed by the animal from a particular location. The codings of events with cues that are so far apart that they cannot be viewed within a Hebbian time window may be considered distinct episodes. Other cells are viewed to encode the common cues that are experienced across episodes and have the capacity to bridge overlapping episodic representations. This model is envisioned to support a rat's ability to "navigate," that is, to infer "short cuts" and "roundabout routes," after it has had overlapping experiences with all parts of the environment (Sutherland et al., 1987). Notably, these abilities are mediated without metric calculations of distances or angles, that is, without a "map." Rather, they are reflections of relational and inferential memory expression within a constrained framework of associations defined by the relevant spatial relationships. Consistent with this view, the hippocampus is critical to performance mediated by navigational inferences (Eichenbaum et al., 1990).

Inferential Expression of Nonspatial Memories. Several studies have shown that the hippocampus is critical for the learning and flexible expression of nonspatial stimulus relations (see Bunsey and Eichenbaum, 1995, 1996; Eichenbaum and Bunsey, 1995). In one study, we showed that the hippocampus is required for the acquisition and flexible, inferential expression of an orderly series of odor relationships (Dusek and Eichenbaum, 1997). Subjects learned a set of pairwise "premises": A $>$ B, then B $>$ C, then C $>$ D, then D $>$ E, where the rats were trained to select items to the left of the "$>$" over those on the right. Intact rats readily acquired

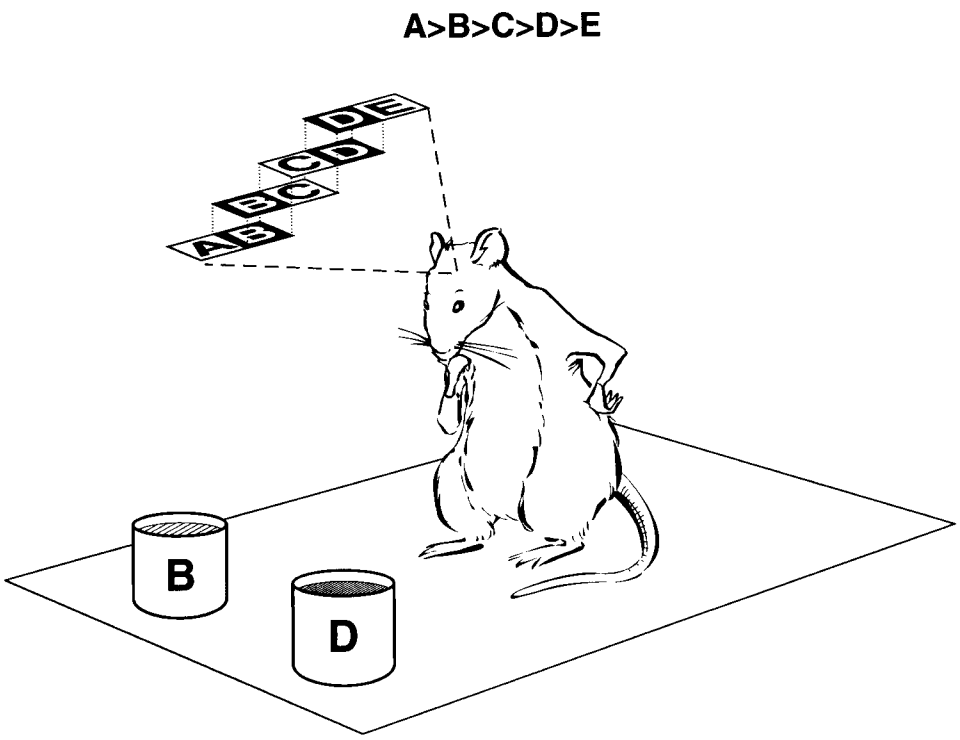

Figure 7. Transitive Inference in Serial Ordering

Representation of an odor series by cells that represent each trained odor pairing, plus nodal representations (dotted lines) of odors that are common between some of the trained pairings.

the premises and, most importantly, could infer the appropriate transitive relationship between nonadjacent stimuli B and D (if B $>$ C and C $>$ D, then B $>$ D). Following hippocampal disconnection, rats learned the four premise problems but showed no capacity for inference about indirectly related items.

In our model of this problem, distinct sets of hippocampal cells encode events and sequences for the pairwise cue relationships trained in distinct episodes (Figure 7). In addition, the commonalities of the odor cues experienced across distinct episodes would be captured by nodal representations. Assuming the nodal representations of B and D are activated by the transitive challenge, these activations could link the overlapping representations of the BC and CD episodes. Thus, the same structure of memory space that mediates spatial navigation can also be seen to support "navigation" among conceptual relations within a memory space for a serial ordering of odors.

Memory Consolidation

The early findings on human amnesia demonstrated that, in addition to the pervasive impairment in new learning, hippocampal damage results in the loss of memories acquired prior to the surgery. Moreover, the retrograde amnesia is graded—the loss is most severe for memories acquired recently before the surgery, whereas general knowledge obtained early in life and memories of childhood experiences remain intact. These observations led to the suggestion that the hippocampus plays a time-limited role in which its processing mediates the consolidation of memories elsewhere in the brain, presumably in the cerebral cortex (see Milner et al., 1998). The present conceptual framework can be extended to provide a preliminary account for hippocampal consolidation of cortical memories.

The hippocampus is an integral component of a memory system that involves widespread areas of the neocortex, the parahippocampal cortical region (composed of the perirhinal and parahippocampal cortex), and the hippocampus itself. Connections within this set of structures involve bidirectional pathways between the cortex and hippocampal region that support considerable two-way interactions, and several theoretical models have suggested that memory consolidation is mediated through these interactions (reviewed by Squire and Alvarez, 1995; Nadel and Moscovitch, 1997). The present conceptual framework offers potential mechanisms for the cortical–hippocampal interplay proposed to mediate memory consolidation.

The development of event and sequence representations in the hippocampus is conceived to occur within one or a few trials, and the development of nodal codings parallels the variations in experience that occur across related episodes. We propose that consolidation begins with interactions between the hippocampus and the parahippocampal region. Parahippocampal neurons receive direct inputs from many cortical areas, and so they would be expected to encode the configurations of stimuli to compose event representations based on simultaneity of these inputs alone. In addition, parahippocampal neurons have an unusual capacity for prolonged firing following discrete events (Suzuki et al.,

1997; Young et al., 1997). So cells in this region may rapidly support the coding of event sequences in the intrinsic population, supporting some associations between closely sequenced cues (Bunsey and Eichenbaum, 1993). However, because of the very high level of interconnectivity of hippocampal pyramidal cells relative to that in all the cortical areas, the development of sequence and nodal representations is envisioned as primarily in the hippocampus shortly after learning.

Thus, for some period after learning, the associations of event representations in the parahippocampal region depend on the connections to and from the hippocampus. At the same time, feedback from the hippocampus is envisioned to mediate the development of sequence and nodal representations within the parahippocampal region by providing an indirect pathway that drives the coactivation of parahippocampal neurons, enhancing the connections within their intracortical network. When sequence and nodal cell properties have been acquired by parahippocampal cells, the memory can be considered to have consolidated there, in the sense that the memory abilities conferred by these cells would no longer require hippocampal feedback. The final stage of consolidation involves a similar interplay between the cortical association areas and the parahippocampal region. Initially, cortical associations are seen to depend on the parahippocampal region to supply linkages between their representations. By simultaneously driving cells in cortical areas and activating their intracortical connections, these linkages would be expected to mediate the ultimate development of sequence and nodal properties in the cortical association areas. When this is accomplished, the entire hippocampal circuit would no longer be necessary for the existence of event, sequence, and nodal representations. Consistent with the proposal that consolidation occurs in stages involving first a consolidation within the parahippocampal region and then later in the cortex, human amnesics with damage extending into the parahippocampal region have a more extended retrograde amnesia than those with selective hippocampal damage (Rempel-Clower et al., 1996).

The key aspects of this model involve the unusual associational structure of hippocampal anatomy that make it the earliest site for arbitrary associations that underlie event, sequence, and nodal properties. At the earliest stages of parahippocampal or neocortical processing, the range of associations and the speed of their formation may be much more limited, but they can mediate substantial development and reorganization of a memory space through the connections within the hippocampus initially. In this way, the repeated invocation of hippocampal representations onto the cortex serves to reorganize cortical representations accommodating new information and new associations within the overall knowledge structure encoded there.

This integrative processing, involving the interleaving of new representations among the existing structure, can be seen to benefit the cortical memory organization for a very long period (McClelland et al., 1995). Indeed, contrary to recent suggestions (Nadel and Moscovitch, 1997), memory reorganization is seen as a prolonged process. From this view, the "completion" of consolidation is seen as a state at which integration of a new memory is asymptotic, that is, a state in which new experiences do not alter the relevant parts of the overall memory organization. When this state is achieved, removal of the hippocampus would not be expected to affect the operation of the cortical network. For some types of memory, this might be achieved within days or weeks (Winocour, 1990; Zola-Morgan and Squire, 1990; Kim and Fanselow, 1992). Other memory experiences might benefit by integration with earlier formed memories over months or years (Corkin, 1984). Thus, the duration of consolidation is dependent on the nature of the learned material in terms of how many appropriate linkages across experience will benefit subsequent retrieval. To the extent that these are few and repeated frequently, consolidation will be completed readily. To the extent that memory for unique episodes benefits by linkage with many related episodes and facts, or continues to be reshaped by new experience, consolidation could go on for a lifetime.

Conclusions

This review began by summarizing observations on amnesia consequent to hippocampal region damage in humans, and contrasted the broad scope of memory involved in these cases with the narrow range of spatial processing implicated by the cognitive map hypothesis. In considering the breadth of the cognitive mapping hypothesis, it is important to clarify the potential ambiguity in the term "cognitive map." This could refer to a systematic representation (a "mapping") of any set of cognitive features or events. This conception is sufficiently general that it could encompass the broad range of findings on amnesia in animals and humans, as well as the view on hippocampal cells that is presented here. This view is also consistent with Tolman's (1949) extension of the properties of cognitive maps as mediating expectancies and inferences in a more general way. However, this is not the conception used to describe the nature of hippocampal representations in the initial (O'Keefe and Nadel, 1978) or more recent (McNaughton et al., 1996; Muller, 1996) versions of cognitive map theory. In those accounts, the term "cognitive map" refers to a mental (cognitive) representation of physical space (a map), following the original description by Tolman (1948). The present accounting most directly addressed the schemes that involve dedicated, systematic mappings of physical space (O'Keefe and Nadel, 1978; Burgess and O'Keefe, 1996; McNaughton et al., 1996). A consideration of other proposals about the spatial functions of the hippocampus will provide the context in which we will summarize our findings.

Some have argued that hippocampal processing is fundamentally spatial but have remained silent on whether spatial memory is based on a systematic mapping or some other form of spatial representation (e.g., Nadel, 1991; Jarrard, 1993). The present review concludes that any apparent "primacy" for spatial representation is a direct consequence of the ever-present spatial regularities associated with behavioral episodes. Locations where events occur almost always provide significant regularities that can be incorporated into most of the event codings. At the same time, we emphasize that nonspatial events are incorporated in situations

where they occur with regularity and can provide a pervasive influence when the events occur across many places (Wood et al., 1999).

Sometimes this notion of the cognitive map has been *expanded* or *linked* to a more general function. For example, Muller (1996) acknowledged that cognitive mapping may be only a specific example of a more general hippocampal function, although he did not specify how geometric properties would translate into, or serve, a more general function, and he suggested that cognitive mapping is the predominant mode of rodent hippocampal processing. O'Keefe and Nadel (1978; see also Nadel, 1991; O'Keefe, 1991) suggested that the notion of an abstract spatial-like mapping of language might exist in the left hippocampus of humans. Nevertheless, when describing the domain of cognitive mapping mediated by the hippocampus, Nadel (1991) insisted that, for animals, "we were referring to space, and we meant space, not abstractly, but concretely" (p. 228). Also, some models of hippocampal spatial function have acknowledged that spatial representation is only a part of a general memory function mediated by the hippocampus (Nadel et al., 1985; McNaughton et al., 1996). However, according to this view, space provides a critical contextual background for encoding or retrieving episodic memories, and these models presume the spatial–contextual contribution is in the form of a cognitive map. Thus, these models do not provide a significant deviation from the original scheme of the dedicated spatial map. Among models of spatial mapping, our account is most similar to Muller et al.'s (1996) conception of "cognitive graphs" arising from the Hebbian binding of adjacent place representations according to the inherent temporal proximity of their activations as rats move through space. Muller noted that nonspatial information could similarly be associated according to temporal relations, as we describe here for the linking of sequential events.

The present conception of a hippocampal memory space provides an alternative to all variants of the cognitive map hypothesis in which space is the organizing principle. While rejecting the notion of a systematic and cohesive spatial mapping, the present review provides compelling support for the existence of place cells. Many hippocampal cells encode the locations where events occur, and the activity of some cells reflects the full topology of the environment independent of the animal's behavior and nonspatial information. However, in our view, true place cells are simply an example of the nodal codings that can identify past episodes that share a common event—in this case, a "place" experienced in the past. In this conception, other nodal codings, including those for a particular stimulus, similarly serve primarily as links to past episodes and not as parts of a spatial map. Nor are they used to navigate, except in the sense that memories for previous places and paths taken, as well as for the events that occurred in familiar locations, are useful for navigation and other forms of inferential memory expression.

Our proposal is strongly consistent with other views of the hippocampus as organizing representations in time (Levy, 1996; Wallenstein et al., 1998) and as capable of using a general autoassociative mechanism to retrieve entire episodes (Marr, 1971; Recce and Harris, 1996; Rolls, 1996; Lisman, 1999). In addition, our model uses the notion of nodal codings to add the ability for linking episodes according to a range of consequential relationships among items in memory (Alvarez and Squire, 1994; McClelland et al., 1995). Within the present conception, the spatial environment is not explicitly "mapped" but is represented only in terms of views and activities that occur in a combined spatial–temporal sequence, or distinct action sequences that are linked by a common location.

Furthermore, the present model is distinguished from spatial mapping theories in that it offers a set of general principles that accounts for both spatial and nonspatial memory dependent on the hippocampus. First, the combination of diverse and distinctive input gradients plus Hebbian mechanisms for encoding coactive inputs mediates the development of a range of specificities for an exceedingly broad range of attended information encoded by hippocampal cells. Second, the organizing principle for these codings is the temporal sequence of events that make up behavioral episodes. Those cells whose activity reflects the most highly specific conjunctions of cues and actions encode rare events that are elements of unique behavioral episodes. Other hippocampal cells whose activity reflects sequences of events serve to link large sets of successive events into representations of episodes that are unique in behavioral significance. When fully established, these representations may mediate the recall of event sequences that compose an episode in memory and disambiguate episodes with common information. Third, other cells whose activity reflects common nodal events among many episodes serve to link distinct episodes that share common events. The combination of linked episodes constitutes a higher-order framework or memory space that may mediate relational processing of indirect associations and inferential judgments about information acquired across episodes. The organization of the memory space is identical for both its spatial and nonspatial information content. In this context, place cells are prevalent codings that might link one's current location to memories for previous episodes at those locations. Fourth, the bidirectional connections between the hippocampal network, the parahippocampal region, and the cortex could mediate the gradual development of sequence and nodal representations in the cerebral cortex. Through a prolonged process of reactivations of the extended network, this could serve to reorganize cortical representations such that they ultimately subserve relational processing even without hippocampal mediation.

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References

Alvarez, P., and Squire, L.R. (1994). Memory consolidation and the medial temporal lobe: a simple network model. Proc. Natl. Acad. Sci. USA *91*, 7041–7045.

Amaral, D.G., and Witter, M.P. (1989). The three-dimensional organization of the hippocampal formation: a review of anatomical data. Neuroscience *31*, 571–591.

Anderson, R.A. (1995). Coordinate transformations and motor planning in the posterior parietal cortex. In The Cognitive Neurosciences, M. Gazzaniga, ed. (Cambridge, MA: MIT Press), pp. 519–548.

Berger, T.W., and Thompson, R.F. (1978). Neuronal plasticity in the limbic system during classical conditioning of the rabbit nictitating membrane response. I. The hippocampus. Brain Res. *145*, 323–346.

Berger, T.W., Alger, B.E., and Thompson, R.F. (1976). Neuronal substrates of classical conditioning in the hippocampus. Science *192*, 483–485.

Berger, T.W., Rinaldi, P.C., Weisz, D.J., and Thompson, R.F. (1983). Single-unit analysis of different hippocampal cell types during classical conditioning of rabbit nictitating membrane response. J. Neurophysiol. *50*, 1197–1219.

Bliss, T.V.P., and Lynch, M.A. (1988). Long term potentiation of synaptic transmission in the hippocampus: properties and mechanisms. In Long Term Potentiation: From Biophysics to Behavior, S.A. Deadwyler and P. Landfield, eds. (New York: A. R. Liss), pp. 3–72.

Blum, K.I., and Abbott, L.F. (1995). A model of spatial map formation in the hippocampus of the rat. Neural Comput. *8*, 85–93.

Bostock, E., Muller, R.U., and Kubie, J.L. (1991). Experience-dependent modifications of hippocampal place cell firing. Hippocampus *1*, 193–206.

Bunsey, M., and Eichenbaum, H. (1993). Paired associate learning in rats: critical involvement of the parahippocampal region. Behav. Neurosci. *107*, 740–747.

Bunsey, M., and Eichenbaum, H. (1995). Selective damage to the hippocampal region blocks long-term retention of a natural and nonspatial stimulus–stimulus association. Hippocampus *5*, 546–556.

Bunsey, M., and Eichenbaum, H. (1996). Conservation of hippocampal memory function in rats and humans. Nature *379*, 255–257.

Bures, J., Fenton, A.A., Kaminsky, Y., and Zinyuk, L. (1997). Place cells and place navigation. Proc. Natl. Acad. Sci. USA *94*, 343–350.

Burgess, N., and O'Keefe, J. (1996). Neuronal computations underlying the firing of place cells and their role in navigation. Hippocampus *7*, 749–762.

Cho, Y.H., Giese, K.P., Tanila, H., Silva, A.J., and Eichenbaum, H. (1998). Abnormal hippocampal spatial representations in αCaMKII^{T286A} and CREB$^{\alpha\Delta-}$ mice. Science *279*, 867–869.

Cohen, N.J., and Eichenbaum, H. (1993). Memory, Amnesia, and the Hippocampal System (Cambridge, MA: MIT Press).

Corkin, S. (1984). Lasting consequences of bilateral medial temporal lobectomy: clinical course and experimental findings in H. M. Semin. Neurol. *4*, 249–259.

Cressant, A., Muller, R.U., and Poucet, B. (1997). Failure of centrally placed objects to control the firing fields of hippocampal place cells. J. Neurosci. *17*, 2531–2542.

Deadwyler, S.A., Bunn, T., and Hampson, R.E. (1996). Hippocampal ensemble activity during spatial delayed-nonmatch-to-sample performance in rats. J. Neurosci. *16*, 354–372.

Dusek, J., and Eichenbaum, H. (1997). The hippocampus and memory for orderly stimulus relations. Proc. Natl. Acad. Sci. USA *94*, 7109–7114.

Eichenbaum, H. (1997). Declarative memory: insights from cognitive neurobiology. Annu. Rev. Psychol. *48*, 547–572.

Eichenbaum, H., and Bunsey, M. (1995). On the binding of associations in memory: clues from studies on the role of the hippocampal region in paired associate learning. Curr. Dir. Psychol. Sci. *4*, 19–23.

Eichenbaum, H., Kuperstein, M., Fagan, A., and Nagode, J. (1987). Cue-sampling and goal-approach correlates of hippocampal unit activity in rats performing an odor discrimination task. J. Neurosci. *7*, 716–732.

Eichenbaum, H., Wiener, S.I., Shapiro, M., and Cohen, N.J. (1989). The organization of spatial coding in the hippocampus: a study of neuronal ensemble activity. J. Neurosci. *10*, 331–339.

Eichenbaum, H., Stewart, C., and Morris, R.G.M. (1990). Hippocampal representation in spatial learning. J. Neurosci. *10*, 331–339.

Feigenbaum, J.D., and Rolls, E.T. (1991). Allocentric and egocentric information processing in the hippocampal formation of the behaving primate. Psychobiology *19*, 21–40.

Foster, T.C., Castro, C.A., and McNaughton, B.L. (1989). Spatial selectivity of rat hippocampal neurons: dependence on preparedness for movement. Science *244*, 1580–1582.

Fox, S.E., and Ranck, J.B., Jr. (1975). Localization and anatomical identification of theta and complex spike cells in dorsal hippocampal formation of rats. Exp. Neurol. *49*, 299–313.

Fried, I., MacDonald, K.A., and Wilson, C.L. (1997). Single neuron activity in human hippocampus and amygdala during recognition of faces and objects. Neuron *18*, 753–765.

Funahashi, S., Bruce, C.J., and Goldman-Rakic, P.S. (1989). Mnemonic coding of visual space in the monkey's dorsolateral prefrontal cortex. J. Neurophysiol. *61*, 331–349.

Gavrilov, V.V., Wiener, S.I., and Berthoz, A. (1998). Discharge correlates of hippocampal complex spike neurons in behaving rats passively displaced on a mobile robot. Hippocampus *8*, 475–490.

Gluck, M., and Myers, C. (1993). Hippocampal mediation of stimulus representation: a computational theory. Hippocampus *3*, 491–516.

Gothard, K.M., Skaggs, W.E., Moore, K.M., and McNaughton, B.L. (1996a). Binding of hippocampal CA1 neural activity to multiple reference frames in a landmark-based navigation task. J. Neurosci. *16*, 823–835.

Gothard, K.M., Skaggs, W.E., and McNaughton, B.L. (1996b). Dynamics of mismatch correction in the hippocampal ensemble code for space: interaction between path integration and environmental cues. J. Neurosci. *16*, 8027–8040.

Halgren, E., Babb, T.L., and Crandal, P.H. (1978). Activity of human hippocampal formation and amygdala neurons during memory testing. EEG Clin. Neurophysiol. *45*, 585–601.

Hampson, R.E., Heyser, C.J., and Deadwyler, S.A. (1993). Hippocampal cell firing correlates of delayed-match-to-sample performance in the rat. Behav. Neurosci. *107*, 715–739.

Hampson, R.E., Byrd, D.R., Konstantopoulos, J.K., Bunn, T., and Deadwyler, S.A. (1996). Hippocampal place fields: relationship between degree of field overlap and cross-correlations within ensembles of hippocampal neurons. Hippocampus *6*, 281–293.

Heit, G., Smith, M.E., and Halgren, E. (1988). Neural encoding of individual words and faces by the human hippocampus and amygdala. Nature *333*, 773–775.

Heit, G., Smith, M.E., and Halgren, E. (1990). Neuronal activity in the human medial temporal lobe during recognition memory. Brain *113*, 1093–1112.

Hetherington, P.A., and Shapiro, M.L. (1993). A simple network model simulates hippocampal place fields: II. Computing goal-directed trajectories and memory fields. Behav. Neurosci. *107*, 434–443.

Hetherington, P.A., and Shapiro, M.L. (1997). Hippocampal place fields are altered by the removal of single visual cues in a distance-dependent manner. Behav. Neurosci. *111*, 20–34.

Huerta, P.T., and Lisman, J.E. (1995). Bidirectional synaptic plasticity induced by a single burst during cholinergic theta oscillation in CA1 in vitro. Neuron *15*, 1053–1063.

Jarrard, L.E. (1993). On the role of the hippocampus in learning and memory in the rat. Behav. Neural Biol. *60*, 9–26.

Jeffrey, K.J. (1998). Learning of landmark stability and instability by hippocampal place cells. Neuropharmacology *37*, 677–687.

Jeffery, K.J., Donnett, J.G., Burgess, N., and O'Keefe, J.M. (1997). Directional control of hippocampal place fields. Exp. Brain Res. *117*, 131–142.

Kentros, C., Hargreaves, E., Hawkins, R.D., Kandel, E.R., Shapiro, M., and Muller, R.V. (1998). Abolition of long-term stability of new hippocampal place cell maps by NMDA receptor blockade. Science *280*, 2121–2126.

Kim, J.J., and Fanselow, M.S. (1992). Modality-specific retrograde amnesia of fear. Science *256*, 675–677.

Knierim, J.J., Kudrimoti, H.S., and McNaughton, B.L. (1995). Place cells, head direction cells, and the learning of landmark stability. J. Neurosci. *15*, 1648–1659.

Knierim, J.J., Kudrimoti, H.S., and McNaughton, B.L. (1998). Interactions between idiothetic cues and external landmarks in the control of place cells and head direction cells. J. Neurophysiol. *80*, 425–446.

Levy, W.B. (1996). A sequence predicting CA3 is a flexible associator that learns and uses context to solve hippocampal-like tasks. Hippocampus *6*, 579–590.

Lisman, J.E. (1999). Relating hippocampal circuitry to function: recall of memory sequences by reciprocal dentate–CA3 interactions. Neuron *22*, 233–242.

Markus, E.J., Barnes, C.A., McNaughton, B.L., Gladden, V.L., and Skaggs, W.E. (1994). Spatial information content and reliability of hippocampal CA1 neurons: effects of visual input. Hippocampus *4*, 410–421.

Markus, E.J., Qin, Y.-L., Leonard, B., Skaggs, W.E., McNaughton, B.L., and Barnes, C.A. (1995). Interactions between location and task affect the spatial and directional firing of hippocampal neurons. J. Neurosci. *15*, 7079–7094.

Marr, D. (1971). Simple memory: a theory for archicortex. Proc. R. Soc. Lond. B Biol. Sci. *262*, 23–81.

McClelland, J.L., McNaughton, B.L., and O'Reilly, R.C. (1995). Why are there complementary learning systems in the hippocampus and neocortex: insights from the successes and failures of connectionist models of learning and memory. Psychol. Rev. *102*, 419–457.

McEchron, M.D., and Disterhoft, J.F. (1997). Sequence of single neuron changes in CA1 hippocampus of rabbits during acquisition of trace eyeblink conditioned responses. J. Neurophysiol. *78*, 1030–1044.

McHugh, T.J., Blum, K.I., Tsien, J.Z., Tonegawa, S., and Wilson, M.A. (1996). Impaired hippocampal representation of space in CA1-specific NMDAR1 knockout mice. Cell *87*, 1339–1349.

McNaughton, B.L., and Morris, R.G.M. (1987). Hippocampal synaptic enhancement and information storage within a distributed memory system. Trends Neurosci. *10*, 408–415.

McNaughton, B.L., Barnes, C.A., and O'Keefe, J. (1983). The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp. Brain Res. *52*, 41–49.

McNaughton, B.L., Chen, L.L., and Markus, E.J. (1991). "Dead reckoning," landmark learning, and the sense of direction: a neurophysiological and computational hypothesis. J. Cogn. Neurosci. *3*, 190–202.

McNaughton, B.L., Barnes, C.A., Gerrard, J.L., Gothard, K., Jung, M.W., Knierim, J.J., Kudrimoti, H., Qin, Y., Skagges, W.E., Suster, M., and Weaver, K.L. (1996). Deciphering the hippocampal polyglot: the hippocampus as a path integration system. J. Exp. Biol. *199*, 173–185.

Mehta, M.R., Barnes, C.A., and McNaughton, B.L. (1997). Experience-dependent, asymmetric expansion of hippocampal place fields. Proc. Natl. Acad. Sci. USA *94*, 8918–8921.

Milner, B., Squire, L.R., and Kandel, E.R. (1998). Cognitive neuroscience and the study of memory. Neuron *20*, 445–468.

Morris, R.G.M. (1990). Does the hippocampus play a disproportionate role in spatial memory? Disc. Neurosci. *VI*, 39–45.

Morris, R.G.M., and Frey, U. (1997). Hippocampal synaptic plasticity: role in spatial learning or the automatic recording of attended experience? Philos. Trans. R. Soc. Lond. B Biol. Sci. *352*, 1489–1503.

Muller, R.U. (1996). A quarter of a century of place cells. Neuron *17*, 813–822.

Muller, R.U., and Kubie, J.L. (1987). The effects of changes in the environment on the spatial firing of hippocampal complex-spike cells. J. Neurosci. *7*, 1951–1968.

Muller, R.U., Kubie, J.L., and Ranck, J.B., Jr. (1987). Spatial firing patterns of hippocampal complex spike cells in a fixed environment. J. Neurosci. *7*, 1935–1950.

Muller, R.U., Bostock, E., Taube, J.S., and Kubie, J.L. (1994). On the directional firing properties of hippocampal place cells. J. Neurosci. *14*, 7235–7251.

Muller, R.U., Stead, M., and Pach, J. (1996). The hippocampus as a cognitive graph. J. Gen. Physiol. *107*, 663–694.

Nadel, L. (1991). The hippocampus and space revisited. Hippocampus *1*, 221–229.

Nadel, L., and Moscovitch, M. (1997). Memory consolidation, retrograde amnesia and the hippocampal complex. Curr. Opin. Neurobiol. *7*, 217–227.

Nadel, L., Wilner, J., and Kurz, E.M. (1985). Cognitive maps and environmental context. In Context and Learning, P. Balsam and A. Tomie, eds. (Hillsdale, NJ: Lawrence Earlbaum Associates), pp. 385–406.

O'Keefe, J.A. (1976). Place units in the hippocampus of the freely moving rat. Exp. Neurol. *51*, 78–109.

O'Keefe, J.A. (1979). A review of hippocampal place cells. Prog. Neurobiol. *13*, 419–439.

O'Keefe, J.A. (1991). An allocentric spatial model for the hippocampal cognitive map. Hippocampus *1*, 230–235.

O'Keefe, J., and Burgess, N. (1996). Geometric determinants of the place fields of hippocampal neurons. Nature *381*, 425–428.

O'Keefe, J.A., and Conway, D.H. (1978). Hippocampal place units in the freely moving rat: why they fire when they fire. Exp. Brain Res. *31*, 573–590.

O'Keefe, J., and Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. Brain Res. *34*, 171–175.

O'Keefe, J.A., and Nadel, L. (1978). The Hippocampus as a Cognitive Map (New York: Oxford University Press).

O'Keefe, J.A., and Speakman, A. (1987). Single unit activity in the rat hippocampus during a spatial memory task. Exp. Brain Res. *68*, 1–27.

Olds, J., Disterhoft, J.F., Segal, M., Kornblith, C.L., and Hirsh, R. (1971). Learning centers of rat brain mapped by measuring latencies of conditioned unit responses. J. Neurophysiol. *35*, 202–219.

Olton, D.S. (1989). Mnemonic functions of the hippocampus: single unit analyses in rats. In The Hippocampus—New Vistas, V. Chan-Palay and C. Kohler, eds. (New York: A. R. Liss), pp. 411–424.

Olton, D.S., Branch, M., and Best, P.J. (1978). Spatial correlates of hippocampal unit activity. Exp. Neurol. *58*, 387–409.

Olton, D.S., Becker, J.T., and Handlemann, G.E. (1979). Hippocampus, space, and memory. Brain Behav. Sci. *2*, 313–365.

O'Mara, S.M., Rolls, E.T., Berthoz, A., and Kesner, R.P. (1994). Neurons responding to whole-body motion in the primate hippocampus. J. Neurosci. *14*, 6511–6523.

Ono, T., Nakamura, K., Nishijo, H., and Eifuku, S. (1993). Monkey hippocampal neurons related to spatial and nonspatial functions. J. Neurophysiol. *70*, 1516–1529.

Otto, T., and Eichenbaum, H. (1992). Neuronal activity in the hippocampus during delayed nonmatch to sample performance in rats: evidence for hippocampal processing in recognition memory. Hippocampus *2*, 323–334.

Perret, D.I., Mistlin, A.J., and Chitty, A.J. (1987). Visual cells responsive to faces. Trends Neurosci. *10*, 358–364.

Quirk, G.J., Muller, R.U., and Kubie, J.L. (1990). The firing of hippocampal place cells in the dark depends on the rat's recent experience. J. Neurosci. *10*, 2008–2017.

Ranck, J.B., Jr. (1973). Studies on single neurons in dorsal hippocampal formation and septum in unrestrained rats. Part I. Behavioral correlates and firing repertoires. Exp. Neurol. *41*, 461–531.

Recce, M., and Harris, K.D. (1996). Memory for places: a navigational model in support of Marr's theory of hippocampal function. Hippocampus *6*, 735–748.

Redish, A.D., and Touretzky, D.S. (1997). Cognitive maps beyond the hippocampus. Hippocampus *7*, 15–35.

Rempel-Clower, N.L., Zola, S.M., Squire, L.R., and Amaral, D.G. (1996). Three cases of enduring memory impairment following bilateral damage to the hippocampal formation. J. Neurosci. *16*, 5233–5255.

Rolls, E.T. (1987). Information representation, processing and storage in the brain: analysis at the single neuron level. In The Neural

and Molecular Bases of Learning, J.-P. Changeux and M. Konishi, eds. (San Diego, CA: Academic Press), pp. 240–265.

Rolls, E.T. (1996). A theory of hippocampal function in memory. Hippocampus *6*, 601–620.

Rolls, E.T., Miyashita, Y., Cahusac, P.M.B., Kesner, R.P., Niki, H., Feigenbaum, J.D., and Bach, L. (1989). Hippocampal neurons in the monkey with activity related to the place in which a stimulus is shown. J. Neurosci. *9*, 1835–1845.

Rose, G.M., and Dunwiddie, T.V. (1986). Induction of hippocampal long-term potentiation using physiologically patterned stimulation. Neurosci. Lett. *69*, 244–248.

Rotenberg, A., Mayford, M., Hawkins, R.D., Kandel, E.R., and Muller, R.U. (1996). Mice expressing activated CaMKII lack low frequency LTP and do not form stable place cells in the CA1 region of the hippocampus. Cell *87*, 1351–1361.

Rotenberg, A., and Muller, R.U. (1997). Variable place-cell coupling to a continuously viewed stimulus: evidence that the hippocampus acts as a perceptual system. Philos. Trans. R. Soc. Lond. B Biol. Sci. *352*, 1505–1513.

Sakurai, Y. (1990). Hippocampal cells have behavioral correlates during performance of an auditory working memory task in the rat. Behav. Neurosci. *104*, 253–263.

Sakurai, Y. (1994). Involvement of auditory cortical and hippocampal neurons in auditory working memory and reference memory in the rat. J. Neurosci. *14*, 2606–2623.

Sakurai, Y. (1996). Hippocampal and neocortical cell assemblies encode memory processes for different types of stimuli in the rat. J. Neurosci. *16*, 2809–2818.

Samsonovich, A., and McNaughton, B. (1997). Path integration and cognitive mapping in a continuous attractor neural network model. J. Neurosci. *17*, 5900–5920.

Scoville, W.B., and Milner, B. (1957). Loss of recent memory after bilateral hippocampal lesions. J. Neurol. Neurosurg. Psychiatry *20*, 11–12.

Segal, M., and Olds, J. (1972). Behavior of units in hippocampal circuit of the rat during learning. J. Neurophysiol. *35*, 680–690.

Segal, M., Disterhoft, J.D., and Olds, J. (1972). Hippocampal unit activity during classical aversive and appetitive conditioning. Science *175*, 792–794.

Shapiro, M.L., and Olton, D.S. (1994). Hippocampal function and interference. In Memory Systems 1994, E. Tulving and D.L. Schacter, eds. (Cambridge, MA: MIT Press), pp. 87–117.

Shapiro, M.L., Tanila, H., and Eichenbaum, H. (1997). Cues that hippocampal place cells encode: dynamic and hierarchical representation of local and distal stimuli. Hippocampus *7*, 624–642.

Sharp, P.E., Kubie, J.L., and Muller, R.U. (1990). Firing properties of hippocampal neurons in a visually symmetrical environment: contributions of multiple sensory cues and mnemonic processes. J. Neurosci. *10*, 3093–3105.

Sharp, P.E., Blair, H.T., Etkin, D., and Tzanetos, D.B. (1995). Influences of vestibular and visual motion information on the spatial firing patterns of hippocampal place cells. J. Neurosci. *15*, 173–189.

Shen, J., Barnes, C.A., McNaughton, B.L., Skaggs, W.E., and Weaver, K.L. (1997). The effect of aging on experience-dependent plasticity of hippocampal place cells. J. Neurosci. *17*, 6769–6782.

Skaggs, W.E., and McNaughton, B.L. (1998). Spatial firing properties of hippocampal CA1 populations in an environment containing two visually identical regions. J. Neurosci. *18*, 8455–8466.

Squire, L.R., and Alvarez, P. (1995). Retrograde amnesia and memory consolidation: a neurobiological perspective. Curr. Opin. Neurobiol. *5*, 169–177.

Squire, L.R., Knowlton, B., and Musen, G. (1993). The structure and organization of memory. Annu. Rev. Psychol. *44*, 453–495.

Sutherland, R.J., Chew, G.L., Baker, J.C., and Linggard, R.C. (1987). Some limitations on the use of distal cues in place navigation by rats. Psychobiology *15*, 48–57.

Suzuki, W.A., Miller, E.K., and Desimone, R. (1997). Object and place memory in the macaque entorhinal cortex. J. Neurophysiol. *78*, 1062–1081.

Tanaka, K., Saito, H., Fukada, Y., and Moriya, M. (1991). Coding visual images of objects in the inferotemporal cortex of the macaque monkey. J. Neurosci. *6*, 134–144.

Tanila, H., Carlson, S., Linnankoski, I., and Kahila, H. (1993). Regional distribution of functions in dorsolateral prefrontal cortex of the monkey. Behav. Brain Res. *53*, 63–71.

Tanila, H., Shapiro, M., Gallagher, M., and Eichenbaum, H. (1997a). Brain aging: impaired coding of novel environmental cues. J. Neurosci. *17*, 5167–5174.

Tanila, H., Shapiro, M.L., and Eichenbaum, H.E. (1997b). Discordance of spatial representation in ensembles of hippocampal place cells. Hippocampus *7*, 613–623.

Tanila, H., Sipila, P., Shapiro, M., and Eichenbaum, H. (1997c). Brain aging: changes in the nature of information coding by the hippocampus. J. Neurosci. *17*, 5155–5166.

Thompson, L.T., and Best, P.J. (1989). Place cells and silent cells in the hippocampus of freely-behaving rats. J. Neurosci. *9*, 2382–2390.

Thompson, L.T., and Best, P.J. (1990). Long-term stability of place-field activity of single units recorded from the dorsal hippocampus of freely behaving rats. Brain Res. *509*, 299–308.

Tolman, E.C. (1948). Cognitive maps in rats and men. Psychol. Rev. *55*, 189–208.

Tolman, E.C. (1949). There is more than one kind of learning. Psychol. Rev. *56*, 144–155.

Vargha-Khadem, F., Gadian, D.G, Watkins, K.E., Connelly, A., Van Paesschen, W., and Mishkin, M. (1997). Differential effects of early hippocampal pathology on episodic and semantic memory. Science *277*, 376–380.

Wallenstein, G.V., Eichenbaum, H., and Hasselmo, M.E. (1998). The hippocampus as an associator of discontiguous events. Trends Neurosci. *21*, 315–365.

Wible, C.G., Findling, R.L., Shapiro, M., Lang, E.J., Crane, S., and Olton, D.S. (1986). Mnemonic correlates of unit activity in the hippocampus. Brain Res. *399*, 97–110.

Wiener, S.I., Paul, C.A., and Eichenbaum, H. (1989). Spatial and behavioral correlates of hippocampal neuronal activity. J. Neurosci. *9*, 2737–2763.

Wiener, S.I., Korshunov, V.A., Garcia, R., and Berthoz, A. (1995). Inertial, substratal and landmark cue control of hippocampal CA1 place cell activity. Eur. J. Neurosci. *7*, 2206–2219.

Willshaw, D.J., and Buckingham, J.T. (1990). An assessment of Marr's theory of the hippocampus as a temporary memory store. Philos. Trans. R. Soc. Lond. B Biol. Sci. *329*, 205–215.

Wilson, M., and McNaughton, B.L. (1993). Dynamics of the hippocampal ensemble code for space. Science *261*, 1055–1058.

Winocour, G. (1990). Anterograde and retrograde amnesia in rats with dorsal hippocampal or dorsomedial thalamic lesions. Behav. Brain Res. *38*, 145–154.

Wood, E.R., Dudchenko, P.A., and Eichenbaum, H. (1999). The global record of memory in hippocampal neuronal activity. Nature *397*, 613–616.

Worden, R. (1992). Navigation by fragment fitting: a theory of hippocampal function. Hippocampus *2*, 165–188.

Young, B.J., Fox, G.D., and Eichenbaum, H. (1994). Correlates of hippocampal complex-spike cell activity in rats performing a non-spatial radial maze task. J. Neurosci. *14*, 6553–6563.

Young, B.J., Otto, T., Fox, G.D., and Eichenbaum, H. (1997). Memory representation within the parahippocampal region. J. Neurosci. *17*, 5183–5195.

Zola-Morgan, S.M., and Squire, L.R. (1990). The primate hippocampal formation: evidence for a time-limited role in memory storage. Science *250*, 288–290.

Zola-Morgan, S.M., Squire, L.R., and Amaral, D.G. (1986). Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. J. Neurosci. *6*, 2950–2967.